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THE RENAL CHANGES IN RABBITS INOCULATED WITH STREPTOCOCCI *

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A number of writers have commented on the difficulties in producing chronic nephritis in animals.

Ophüls[1] says "a very serious obstacle to experiments of this kind is the spontaneous occurrence of chronic nephritis in the animals used. Even in rodents, chronic nephritis does occasionally occur spontaneously." And Pearce[2] says: "It must be admitted that the experimental study of nephritis supports the more common conception of the etiology of chronic nephritis in man, that is, that it is a gradually developing lesion due to long continued insidious action of some ill defined toxic substance. With the possible exception of Dickson, the results obtained have been neither constant nor of such nature as to justify the term of chronic nephritis. Occasional positive findings, in view of the frequency of spontaneous lesions, must be regarded with suspicion." Dickson[3] also remarks that "a review of the literature on experimentally produced chronic nephritis forces one to the conclusion that the results obtained have not been very satisfactory."

In the article on experimental cardiorenal disease by Christian, Smith and Walker,[4] mention is made by Smith of his examination of the kidneys of normal rabbits as controls. It is unfortunate that a more detailed account is not given by Smith of the conditions in these kidneys since his examination is one of the few that concern so considerable a number of normal rabbit kidneys. Smith's statement is: "The lesions when found consisted in almost every instance of a single area of round cell infiltration, connective tissue increase or a small group of dilated tubules." He also states that "some lesion is found in 11 of the 50 rabbits." Ophüls and Dickson[5] have also made a careful study of the kidneys of 50 normal rabbits. These animals were partly from the market, partly animals raised in the laboratory. Many had been used in the physiological laboratory and killed immediately after experiments. Several were old rabbits. Concerning the kidneys of these rabbits he says: "Twenty-eight rabbits, among them some old ones, had entirely normal kidneys, 9 showed parenchymatous lesions, 3 a few areas of cellular infiltration. In 10 we found scattered small areas in which were marked interstitial lesions with the formation of small depressions on the surface. Four of these proved to be chronic septic foci which extended from the vicinity of the papilla to the outer surface. In the other 6 the same arrangement of the new-formed connective tissue in narrow radial bands which start deep in the pyramids was noticeable although no evidence of a septic infection could be discovered. The interstitial lesions were accom-

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* Received for publication July 6, 1914.

[1] *Jour. Med. Research*, 1908, 13, p. 497.

[2] *Arch. Int. Med.*, 1910, 5, p. 133.

[3] Ibid., 1909, 3, p. 375.

[4] *Arch. Int. Med.*, 1911, 8, p. 468.

[5] *Proc. Soc., Exper. Biol. and Med.*, 1910-11, 8, p. 75.

panied by marked epithelial lesions in 2 cases only, producing to a certain extent the picture of a chronic parenchymatous nephritis, although the lesions were never very extensive. Lesions of the blood-vessels or primary lesions of the glomeruli were not found in any case."

Ghoreyeb[6] does not state how many rabbits were used altogether in the experiments dealing with mechanical obstruction of the blood-supply of the kidneys. There is, however, mention of 47 and of these 8 had "spontaneous nephropathy." The changes described correspond most with those we have considered as chronic.

More recently Longcope[7] reports the examination of the kidneys of 24 supposedly normal rabbits with the following results: "The kidneys of 16 were absolutely normal, in 4 they showed old fibrous scars in the cortex, . . . and in 4 there were one or two patches of small round cells between the tubules of the cortex — in no instance were glomerular lesions encountered."

A milk epidemic in Chicago of acute angina led to experiments[8] that afforded good opportunity to examine the changes in the kidneys of rabbits inoculated with streptococci isolated from the patients to compare such changes with those in rabbits inoculated with other streptococci and also to study the alterations in the kidneys of rabbits injected with streptococcus vaccine and antistreptococcus serum.

The kidneys of 58 rabbits were examined. Of these 51 were inoculated with hemolytic streptococci; 6 with streptococci isolated from patients with epidemic sore throat, and 1 with streptococcus viridans. Eleven rabbits received antistreptococcic serum either before or after inoculation with living streptococci; 15 received vaccine before inoculation and 2 received both serum and vaccine. The evidences of immunity possessed by these animals have been studied by J. J. Moore,[9] and it may be stated now that there was no particular difference in the lesions in the untreated and the treated animals except that in the latter the changes were fewer and milder.

The tissues were fixed in Zenker's fluid, imbedded in paraffin and stained with hematoxylin and eosin, phosphotungstic acid hematoxylin, polychrome methylene blue and eosin, also by the Giemsa and Wright methods for bacteria. That some statement as to the amount of renal tissue examined might be made, an account was kept of the linear measurement of the external margins of the sections examined from each block. This is readily arrived at by measuring carefully the capsular margin of one section and multiplying it by the number of sections from that block. On an average 52.3 cm. was examined from each rabbit.

Not all the protocols of the experiments need be published; the following will serve to indicate their character:

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[6] *Jour. Exp. Med.*, 1913, 18, p. 29.

[7] Ibid., 1913, 18, p. 678.

[8] Leila Jackson, Experimental rheumatic myocarditis, *Jour. Infect. Dis.*, 1912, 11, p. 243, and Experimental streptococcal arthritis in rabbits, *Ibid.*, 1913, 12, p. 364.

[9] *Jour. Infect. Dis.*, 1914, 15, p. 215.

Rabbit 35-D.—April 2, 1912. Injected intravenously with a 24-hour growth from one blood agar slant of streptococcus (217) isolated from pus obtained from suppurating glands of the neck; death eleven days later.

Autopsy: There are a few small hemorrhages in the endocardium; the heart valves are normal; many of the joints[10] are swollen.

Streptococci in pure culture were obtained from the heart's blood and peritoneal fluid.

In a field of 4.5 mm. in diameter there are forty-six lesions in a medullary pyramid. Some are more or less coalescent, for example in one group there are seven, in another six, in a third four, but most of them are fairly discrete. At one point a number are grouped about a region of necrosis which measures approximately 0.8 mm. across, and in this there are a number of isolated masses of streptococci with rounded contours because the vessels they have occluded are cut across obliquely. In this necrotic region there is very little reaction. Nearly all of these focal lesions consist chiefly of necrotic leukocytes and bacteria. They are on an average about 0.2 mm. in diameter; some of the uriniferous tubules in and about them contain fibrin. There are very few such focal lesions in the cortex. Many of the convoluted tubules in the cortex contain casts, some of which are leukocytic.

In the cortex are acute changes in a few glomeruli with destruction more or less complete of the tuft, also in the intertubular regions the vessels are replaced in a few places by nuclear fragments—masses of material staining with hematoxylin so as to form a blue mesh for the tubules. These alterations are generally in the middle zone of the cortex and in the labyrinth.

Then, too, in the cortex, there are other alterations apparently of longer standing and consisting of perivascular collections of lymphocytes and larger cells[11] about the arcuate as well as the interlobar veins. All stages of emigration of the leukocytes may be seen. Where the cortex is drained by pyramids with changes like those to be described presently, many of the convoluted tubules are dilated and contain hyaline casts.

In the pyramids there are numerous focal lesions, so numerous that in the sections made through a region which (in the sections) has margins measuring 1 cm. on two of the three sides and 0.5 cm. on the third, there are from thirty to forty-five in the various sections. They measure from 30 μ in diameter to a millimeter, this last applying to dimensions parallel with the tubules. They nearly all consist of masses of nuclear debris, in a few the necrosis is characterized by karyolysis, in many bacteria are present in more or less compact masses. Many of these lesions in the pyramid are coalescent. The aggregate capsular margin is 40 cm.

Rabbit 11-M.—Oct. 26, 1912. The rabbit received intravenously one-eighth of the twenty-four-hour growth on one blood agar tube of streptococcus 256.

Oct. 28. Left shoulder joint swollen.
Nov. 3. Swelling about the left shoulder joint decreasing.
Nov. 11. Left shoulder joint markedly swollen.
Dec. 6. Less swelling of left shoulder but rabbit still limps.
Jan. 1, 1913. Killed.

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[10] A description of the changes observed in microscopic preparations of this joint and the joints of other rabbits of this series may be found in the *Jour. Inf. Dis.*, 1913, 12, p. 377.

[11] Many of these cells are in all respects identical with the large cells met with in the myocardium and joint lesions described elsewhere (Jackson).

The cortex is not narrowed and the labyrinth and medullary ray markings are largely absent. In the outer half of the cortex there are many retention cysts—formerly tubules. They are rarely single but several, as many as three or six, occur closely together and some are in contact. The dilatation rarely exceeds twice the size of the area usually presented by sections of the convoluted tubules cut as they are at all possible angles. Some are empty but many contain an eosin staining homogeneous material shrunken away from the lining of greatly flattened cells.

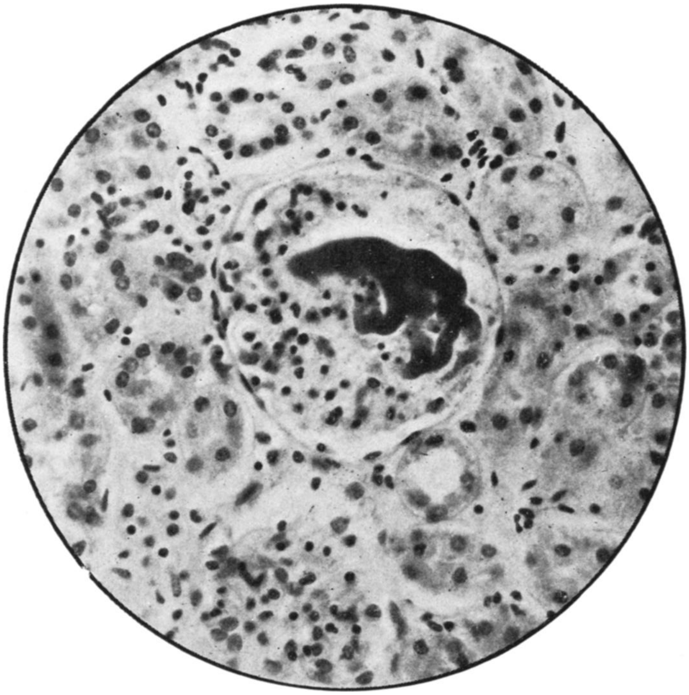

Fig. 1.—A glomerulus in which are masses of cocci filling a group of capillaries. From a rabbit dying 9 days after inoculation. ×325.

The next most pronounced alteration is the presence of small groups of lymphocytes and plasma cells in both cortex and pyramids, more numerous in the latter, where in a field 4.5 mm. in diameter six to eight can be counted, in regions similar in size in the cortex the average is less than one. They are rarely larger than can be contained in the field of the immersion lens and many are smaller. Plasma cells are few, lymphocytes more numerous but most of the cells in these regions appear to belong to the kidney proper. The increase in nuclei, at least in some of these regions, is apparently dependent on the absence of tubules and consequently falling together of stroma and blood-vessels. In these regions and at many places in both pyramid and cortex there are considerable quantities of golden brown pigment in the cells. The pigment is generally found only in the epithelial cells and in places where the changes enumerated occur. Cortical margins measure 49.4 cm.

Vaccine Rabbit 53-M.—Sept. 10, 1913. Injected subcutaneously 500 millions of killed streptococci (256); a similar amount was given on the 14th of September; on the 18th, 750 millions, on the 22d, one billion, and on the 26th, 750 millions.

Oct. 1. Injected intravenously one-tenth of twenty-four-hour growth of living streptococcus 256.

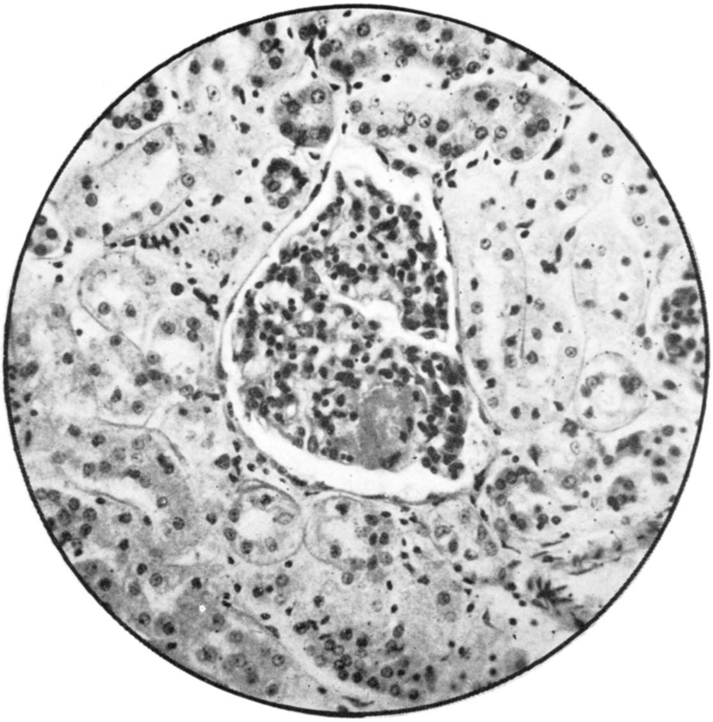

Fig. 2.—A glomerulus containing a hyaline thrombus. From a rabbit dying 7 days after inoculation. × 275.

Oct. 3. No joints involved.

Oct. 4. Metacarpal joints of the right foot swollen.

Oct. 5. Right ankle slightly swollen but rabbit does not limp.

Oct. 10. Joints do not appear worse. Killed.

The lungs and heart appear normal; the spleen is cyanotic; there is coccidiosis of the liver; the kidneys are normal; the right axillary and inguinal lymph glands are enlarged; the right ankle is swollen and there are petechial hemorrhages beneath the skin and extending nearly to the knee; the right wrist is slightly swollen and the surrounding tissues edematous.

There are no changes in the sections except small collections of lymphocytes about some of the large vessels. The cortical exteriors of the sections examined aggregate 94.8 centimeters.

Vaccine Rabbit 27-M.—Jan. 6. Injected subcutaneously 500 millions of killed streptococcus 256; January 8, one billion; January 11, two billions of various strains; again on January 14 and 16; January 18, two billions streptococcus 256.

Jan. 20. The rabbit weighs 3 pounds and 5 ounces.

Feb. 10. No arthritis. Weight 4 pounds and 3 ounces.

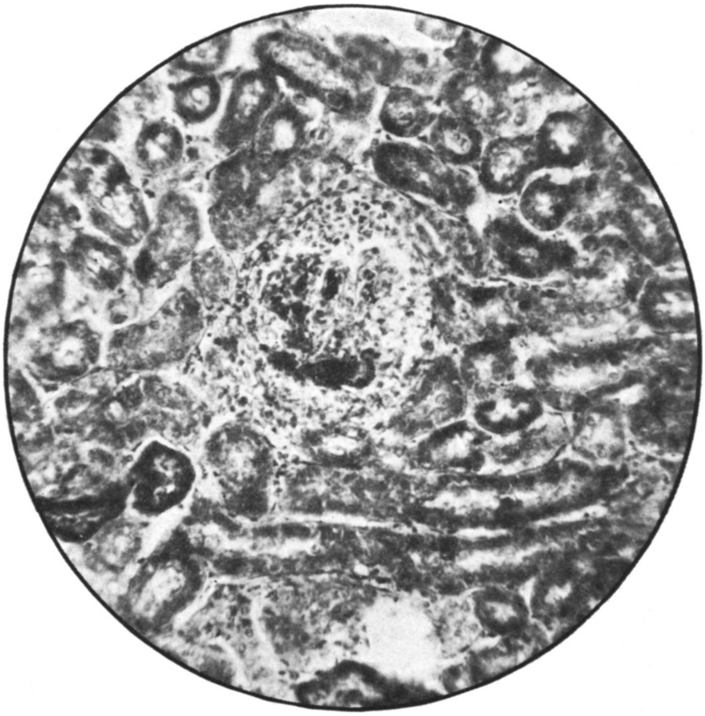

Fig. 3.—Masses of fibrin in a glomerulus. From rabbit dying 7 days after injection. ×200.

March 1. Injected intravenously one-tenth of the twenty-four-hour growth on a blood agar slant of streptococcus 256.

March 3. Aborted during the night.

March 4. Appears sick but there is no arthritis.

March 5. Rabbit dead. Weight is 3 pounds and 10 ounces.

The lungs are normal; there are small hemorrhages along the tricuspid valve; the spleen is greatly enlarged, soft and cyanotic; the liver is fatty; the kidneys and adrenals are normal; the uterus contains pus and the serosa is injected. Streptococci were recovered from the heart's blood, peritoneal fluid and uterus.

There is a spot of necrosis 0.5 mm. in diameter without cellular exudate about a small group of intracapillary masses of cocci in the distal part of a medullary pyramid close to the pelvic mucosa.

In similar situations there are focal lesions 0.2 to 0.4 mm. in diameter, much more numerous, and with characteristics so different that it seems safe to assume that the agents causing them arrived at these places at different times. There are small collections of plasma cells and lymphocytes, the former predominating. The outermost tubules in these places have pyknotic nuclei; those a little nearer the centers are more or less infiltrated with leukocytes, the still more central tubules are altogether replaced by the infiltrating cells. In some of the tubules on the margins there are epithelial cells with dividing nuclei. More extensive and less sharply outlined infiltrations with plasma and lymphocytes are present in the medullary pyramid close to the cortex. For example, in one section 12 lesions coalescent in varying degrees fill a place 2 by 1.6 mm.

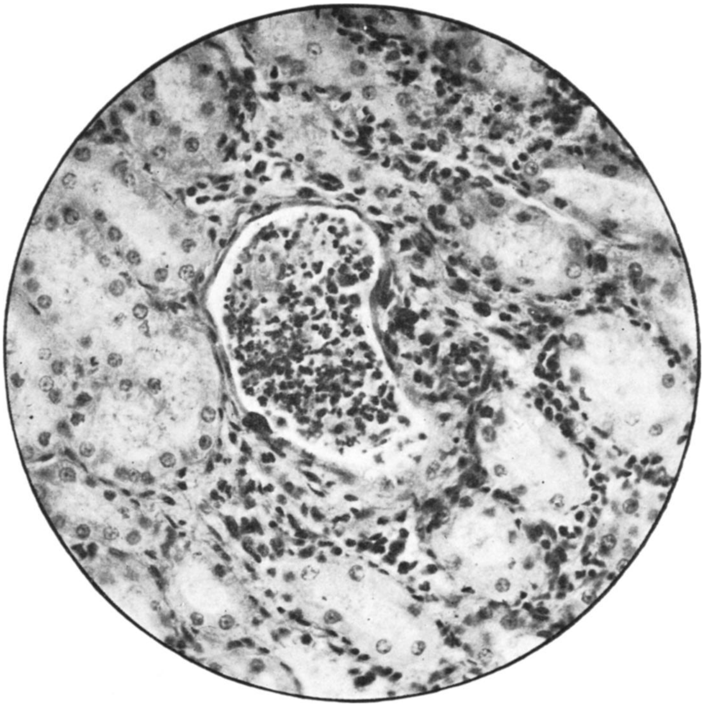

Fig. 4.—An acutely disorganized glomerulus. From rabbit dying 11 days after inoculation. ×250.

There are many aggregations of lymphocytes about the large arcuate veins.

There are very few changes in the cortex. They consist of chronic or subacute lesions in the labyrinths in the middle of the cortex or in its outermost portion, the latter as minute wedge-shaped lesions. The amount of cortex examined is 49.2 cm. measured along the subcapsular margins and including all the sections examined.

Serum Rabbit 17-M.—Nov. 12, 1912. This rabbit received intravenously 1/10 of the 24-hour growth from one blood agar slant of streptococcus 256.

Nov. 15. The left elbow is swollen; 2 c.c. of antistreptococcic serum was given intraperitoneally; again on Nov. 17, 19 and 20.

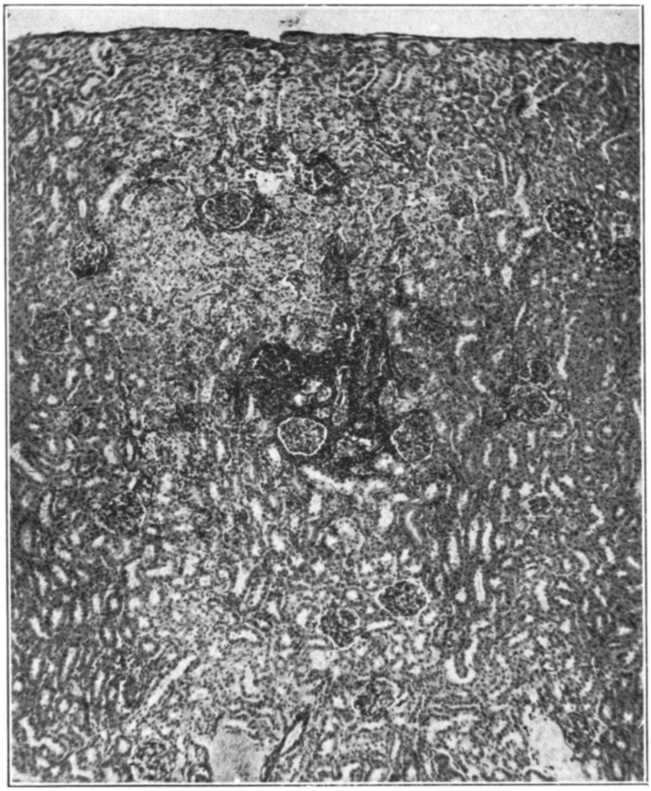

Fig. 5.—A typical subacute focal lesion in the cortex. ×200.

Nov. 21. The rabbit died.

The lungs and heart appear normal; the spleen is swollen and cyanotic; the liver is enlarged and very friable; the kidneys appear normal.

There are practically no changes in 12 sections from the two kidneys; from one the sections have an aggregate cortical margin of 44.2 cm.; those from the other 21.6 cm. About some of the interlobular veins there are small collections of lymphocytes and many are of the large variety. There are also clumps in the vein channels. A few mitotic nuclei are found.

In ten, or 17 percent, of fifty-eight rabbits there were no changes in the sections examined. Acute changes were found in sixteen, or 28 percent, of the rabbits and all but two of these occurred in rabbits dying within eleven days after inoculation. The other two were treated with antistreptococcus serum and died twenty-four and thirty-two days, respectively, after inoculation and in each animal there was a mitral endocarditis. No acute changes were observed in the kidneys of eight rabbits dying of an epidemic, all of which had recovered from the streptococcus infection.

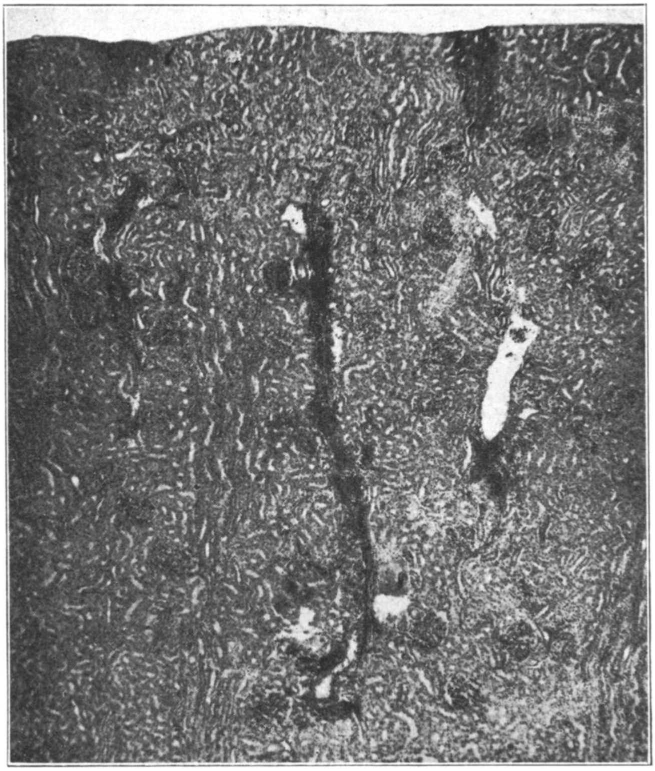

Fig. 6.—An interlobular vein surrounded by lymphocytes and plasma cells. From the kidney of rabbit dying 42 days after inoculation. ×35.

Of the acute lesions intracapillary bacterial emboli (Fig. 1) were most frequent; they were present in eleven rabbits. The number of glomeruli in which bacterial emboli are found varies greatly in different animals. In some, prolonged search is necessary to discover any, while in one case as many as one in every ten glomeruli contains bacterial emboli. The only explanation for the absence of changes in the glomeruli of rabbits observed for long periods is that *these acute lesions heal.* In some animals mycotic emboli occur in all parts of the kidney, in others only in the glomerular loops or in the capillaries of the cortex or medulla, in a few cases only is there necrosis or reaction of the surrounding tissue. Abscesses (Figs. 2 and 3) were found in the kidneys of two rabbits, in one, a five-day rabbit, they were few and small and located in the medulla, in the other, an eleven-day rabbit, they were numerous and small, the largest about 0.2 mm. across, some partially coalescent, others fairly discrete, present in both cortex and medulla. Infarcts were found in the kidneys of two rabbits, and an acute glomerular nephritis in the kidneys of one dying seven days after injection. The lesions in the latter are characterized by large

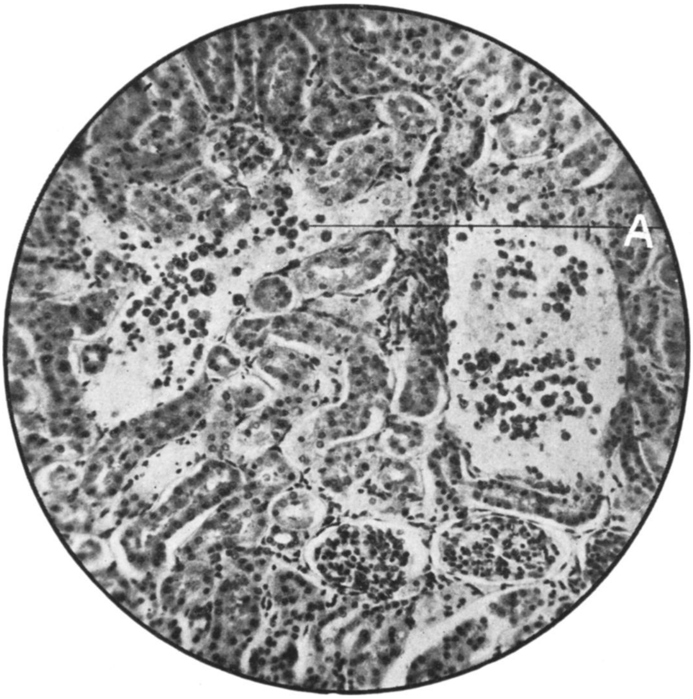

Fig. 7.—Two veins containing more than the normal number of large and small lymphocytes. A. A cell in mitosis. From a rabbit dying 5 days after inoculation. ×160.

masses of cocci in the glomerular loops, hemorrhages into other glomeruli or into the capsular spaces with partially or totally disrupted blood-vessels, masses of fibrin (Figs. 4 and 5) and in some glomerular lesions a more or less cellular exudate.

Subacute changes, lymphocyte and plasma cell exudates (Figs. 6, 7 and 8), were found more frequently than any other alteration, as early as the third day and as late as the one hundred and thirteenth day. They were usually associated with other lesions either acute or chronic. We found them as the only change present in the kidneys of nine rabbits. These exudates are in general small, rarely larger than can be contained in the field of the immersion lens and many smaller. In

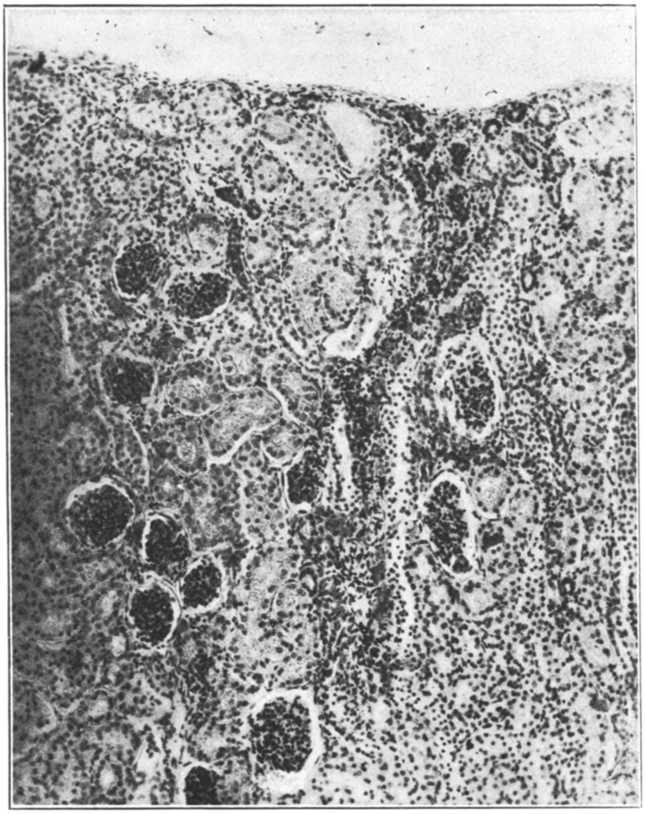

Fig. 8.—A more advanced subacute focal lesion producing slight pitting of the surface. From rabbit dying 16 days after inoculation. ×110.

one case as many as forty are present in 1.5 sq. cm. of pyramidal substance, usually they are much less numerous. They are most often located about blood-vessels, usually veins, and most frequently around the arcuate vessels and vessels in the cortex. Less often they form rather large accumulations filling in defects in the parenchyma, some of them 2 mm. long by 0.5 mm. wide. They are composed almost exclusively of lymphocytes or plasma cells or both, also large endothelioid cells are sometimes present in considerable numbers. Accumulations of plasma cells are somewhat less numerous than those of lymphocytes. In many of the kidneys in which there are exudates about blood-vessels there are in some of the veins more than the normal number of large and small lymphocytes and endothelioid cells

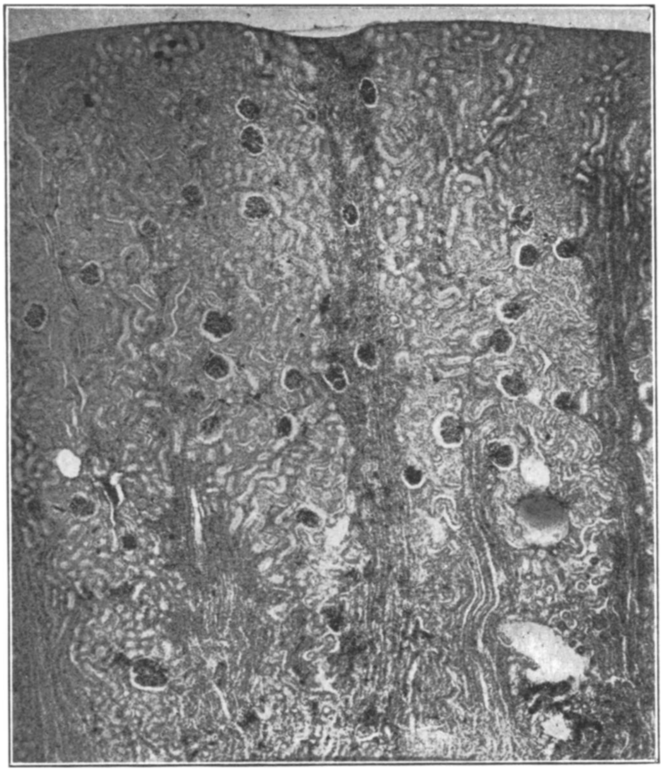

Fig. 9.—A fairly well healed linear scar extending the entire width of the cortex. From Rabbit 16M dying 10 days after injection. ×30.

(Fig. 9). In these cells and also in the cells of the exudate surrounding the vessels mitotic nuclei are occasionally seen and all stages of migration of these cells through the vessel wall can be found.

Changes apparently of still longer duration were found in the kidneys of twenty-two rabbits. These were chiefly small regions where the parenchyma was absent, scars (Figs. 10, 11 and 12), dilated tubules with casts, retention cysts and focal regenerative changes, most of them in animals killed or dying two weeks or more after inoculation. The focal regenerative changes referred to occur in the cortex and consist of dilated tubules lined with a low epithelium sometimes empty, sometimes containing hyaline casts. The scars are usually wedge-

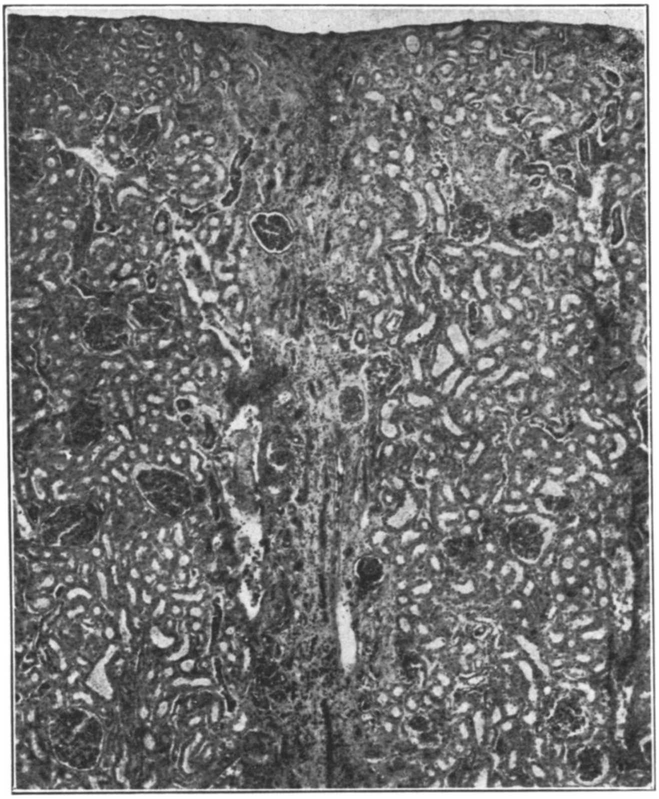

Fig. 10.—An old linear scar in the cortex of Rabbit 14M dying 32 days after inoculation. ×45.

shaped with the base at the capsular margin producing pitting of the surface and extending into the substance for a variable distance, often the entire width of the cortex. A reasonable explanation for the absence of chronic changes in the glomeruli previously referred to is that the acute alterations are quite efficiently repaired.

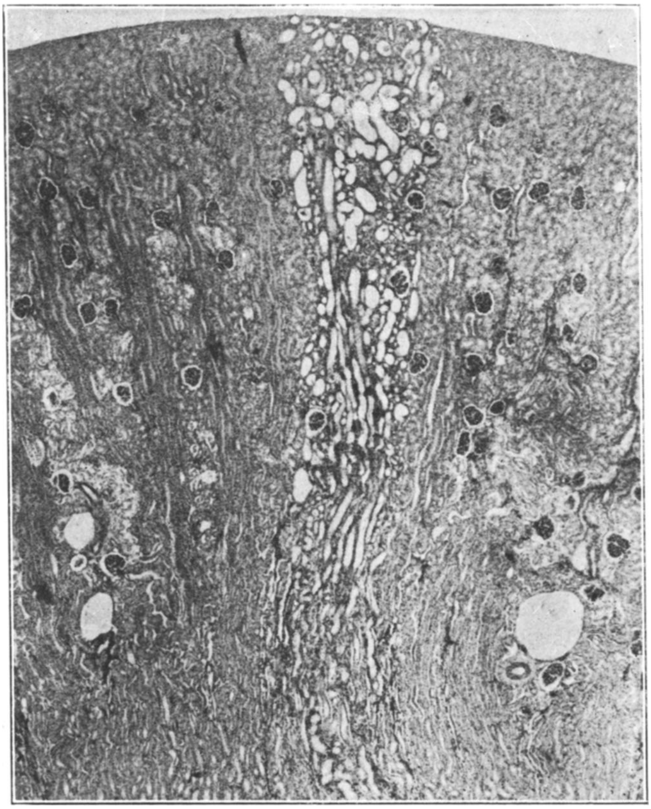

Fig. 11.—A wide region of dilated tubules and retention cysts extending through the cortex into the medulla. From Rabbit 48D killed 136 days after inoculation. ×110.

Changes such as these last described are the only ones we have found in the kidneys of normal rabbits; they correspond well with those described by Smith, Ophüls and Longcope. An exception concerns a glomerulo-nephritis unrelated we believe to the treatment the animal had received.

Oct. 15, 1913. Rabbit 8M was injected intravenously with half the 24-hour growth from one blood agar slant of hemolytic streptococcus 256 isolated from the tonsils of a patient with chronic rheumatism.

Oct. 16. Rabbit appears sick.

Oct. 17. Right wrist swollen and tender.

Oct. 18. Left wrist also swollen.

Oct. 19. Both ankles swollen.

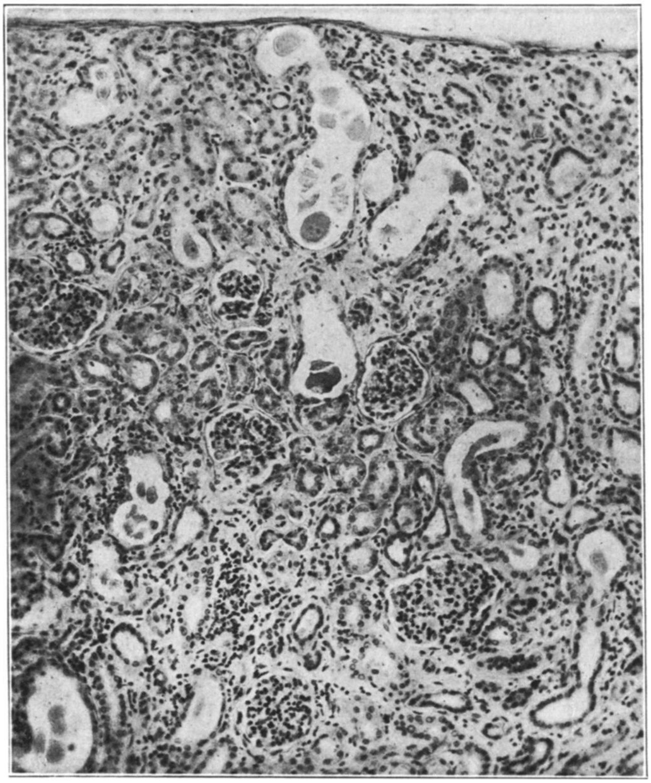

Fig. 12.—Retention cysts in the cortex of Rabbit 11M killed 70 days after inoculation. ×35.

Oct. 22. Left knee involved, cannot walk. Five c.c. of antistreptococcus serum injected into the knee joint, 3 c.c. into the tissues about one of the ankle joints, and 10 c.c. intraperitoneally.

Oct. 24. Died.

The cortex has an even edge with no signs of pitting. It measures 2.5 mm. thick, striations indistinct. Fully three-fourths of the glomeruli are smaller than normal by reason of thickened Bowman's capsules (Fig. 13), and probably collagenous. Of 118 glomeruli 77 had thick capsules. Such glomeruli are most numerous in the outer part of the cortex but a few are deeply located.

For the most part the thickening is three or four times greater than the normal width of the capsule, quite regular and produced by long encircling fibers or spindle-shaped cells. Most of the glomeruli close to the capsule—and there are a good many immediately beneath it—are very small, one-half or two-thirds the normal size; some are no larger than the adjacent uriniferous tubules and all have thickened capsules in varying degrees. Many of the minute glomeruli are rather closely aggregated in triangular-shaped regions, for example, in one such region 0.5 mm. in depth with a margin at the capsular edge 1 mm. long there are 16 such scarred glomeruli. In such places are many plasma cells and the uriniferous tubules remaining are greatly compressed.

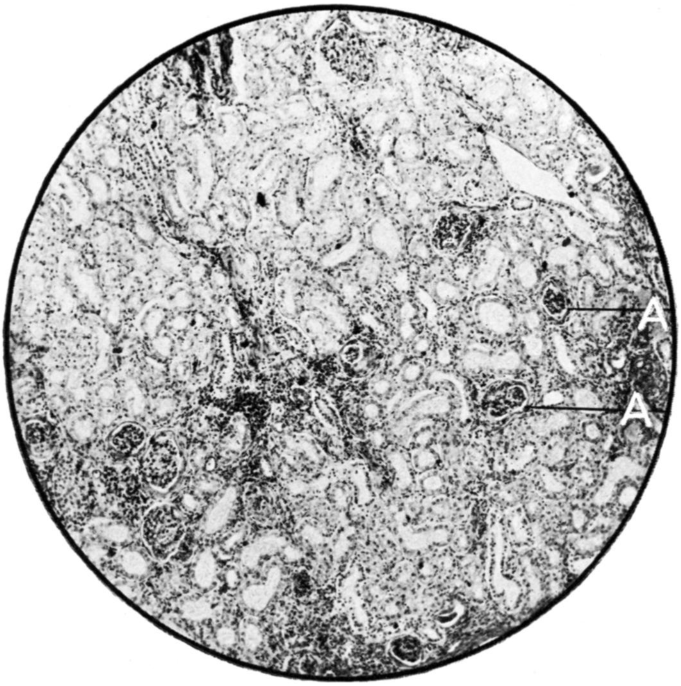

Fig. 13.—Spontaneous chronic glomerulo-nephritis. A. Glomeruli with greatly thickened Bowman's capsules. ×60.

The glomeruli with unchanged capsules have greatly engorged blood vessels, a few have small spaces about them in which plasma coagulated by the fixing agent has accumulated in the capsule. Some of the glomeruli with unchanged capsules are larger than normal. Small masses of fibrin are present in some of their loops. Some capsules contain nothing but red-blood corpuscles. In the medullary pyramids are quite small collections of lymphocytes or lymphocytes with a few plasma cells; they are generally in the boundary zone and so scarce that only one may be found in a section. Many of the convoluted tubules especially in the outer part of the cortex are dilated. There are no changes in the medullary pyramids.

Of the kidneys of normal animals examined by Smith, 11 of 50, or 22 per percent showed alterations; of the same number examined by Ophüls, 22 or 44 percent, contained lesions and of Longcope's 24 rabbits there were changes in the kidneys of 8, or 33 percent. The number of normal kidneys so far examined by us is too small to warrant a statement concerning them except that the kind of lesions found are such as we have included under chronic changes and as yet no subacute lesions have been observed.

Smith does not state in how many animals a particular kind of lesion occurs. Ophüls found areas of cellular infiltration in 3, or 6 percent, and Longcope in 4, or 16.6 per cent, or normal rabbits.

In our experimental animals, lymphocyte and plasma cell exudates were present in thirty-two, or 56.6 percent, from which if we deduct the larger percent (Ophüls — 4 percent) as possibly of other origin, there still remains a considerable number resulting probably from the action of streptococci. The kidneys of twenty-two, or 38.6 percent of the streptococcus rabbits contained chronic changes. Since the majority of the lesions observed by Ophüls, also half of those described by Longcope and all of the changes so far observed by us in normal animals, belong to this type, they can with much less certainty be attributed to the inoculation. If, however, the period of time elapsing after the injection of streptococci into the rabbits from which we examined the kidneys be arbitrarily divided into two periods, one so short that it is fair to assume that sufficient time had not elapsed for chronic changes to develop, and a second period during which such changes are possible, we may arrive at some conclusion as to whether some at least of the more chronic lesions are due to streptococci. Eight, or 25 percent, of the thirty-three rabbits killed or dying within the first two weeks after inoculation have chronic changes in the kidneys, while the kidneys of fifteen, or 62.5 percent, of the twenty-four rabbits living for fifteen to one hundred and eighty-six days after inoculation possess similar alterations. This rather considerable difference in the relative number of kidneys affected with chronic lesions suggests that streptococci may have been the etiologic factor in some instances. Eight animals died of the epidemic referred to. We have been unable to attribute any of the changes mentioned to it, because the changes in the kidneys of these animals were in two of them chronic, in two others subacute and in the remainder no changes were found.

A careful consideration of all of the changes has impressed us with the large percentage of lesions which we have called subacute.

Faulhaber[12] in his search for bacteria in the kidneys of persons dying of acute infectious diseases found focal accumulations of round cells in the outermost layers of the cortex about the glomeruli and blood vessels in 33 of 55 kidneys. He attributes these to the focal presence of bacteria. In his cases of streptococcus infections when these focal lesions were absent bacteria were few.

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[12] *Zieg. Beitr.*, 1891, 10, p. 81

All writers on scarlatinal nephritis have described round cell infiltration in the kidneys. Councilman,[13] who has studied this form of nephritis most carefully, gives the location of the cell accumulations in severe cases as most frequently beneath the capsule and at the bases of the pyramids, in less marked cases as being most numerous and largest at the bases of the pyramids, occasionally forming large masses around the interlobular vessels and less frequently beneath the capsule around the stellate veins. He also observes that these cells, lymphocytes and plasma cells, are found in the vessels as well as in the tissue and that nuclear figures are sometimes found in them. Councilman believes the cells in these exudates must come from the blood vessels.

Schridde,[14] discussing the origin of small cell infiltrations in the kidneys of persons dying of scarlet fever and diphtheria, observes that about the 5th day the capillaries of the medulla contain enormous numbers of lymphocytes, that by the 8th day lymphocytic infiltration is present in both cortex and medulla, derived from emigrated lymphocytes and also containing plasma cells.

Unna[15] and others hold a different opinion regarding the origin of plasma cells. They believe that plasma cells arise from the proliferation of existing cells in the connective tissue.

Lymphocyte and plasma cell exudates in the kidneys of experimental animals have been described by many authors. In 1899 Bonsdorff[16] mentions aggregations of round cells about destroyed tubules and about blood-vessels in the kidneys of rabbits used in which he studied elimination of streptococci. The rabbits on which these observations were made died at intervals varying from 1¼ to 6⅓ days after in inoculation.

Lyon[17] describing the conditions found in the kidneys of rabbits injected with diphtheria toxin makes the following statement: "In the great majority of animals which survive beyond the fourth day there is an accumulation of round cells around some of the cortical vessels. Similar accumulations do not occur in the medulla. This infiltration is always local in character and the degree is variable. Normally there is no layer of lymphoid cells around the large cortical vessels of the rabbit's kidney."

Ophüls[18] notes their presence at the dividing line of cortex and medulla in the kidneys of rabbits treated with bichromate of potash.

Dickson[19] injected guinea-pigs with uranium nitrate; concerning lymphocytic exudates in one of his series he says: "There were distinct areas of round cell infiltration in every case, occurring chiefly near the larger veins at the inner margin of the cortex, but in two cases there was definite infiltration in the regions of damaged glomeruli."

Smith[20] injected rabbits with uranium nitrate and observed that microscopically the most frequent variation from the normal was round cell infiltration, usually small, sometimes of considerable size, the location of which was variable but most often in the cortex near the periphery.

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[13] *Jour. Exper. Med.*, 1898, 3, p. 393.
[14] *Ziegler's Beitr.*, 1913, 55, p. 345.
[15] *Virchow's Archiv*, 1913, 214, p. 321.
[16] *Ziegler's Beitr.*, 1899, 25, p. 188.
[17] *Jour. Path. and Bact.*, 1903-4, 28, p. 430.
[18] *Jour. Med. Research*, 1908, 13, p. 497.
[19] *Arch. Int. Med.*, 1909, 3, p. 375.
[20] *Ibid.*, 1911, 8, p. 468.

Harvey[21] refers to round cell infiltration around damaged glomeruli and tubules in the kidneys of rabbits injected intravenously with para-hydroxy-phenylethylamin. Lymphocytic infiltration in any part of the kidney is noted by O'Hara[22] in rabbits injected subcutaneously with uranium nitrate and intravenously with colon bacilli.

Longcope[23] gives the following account of round cell exudates in the kidneys of rabbits subjected to repeated proteid intoxication. "In the smallest areas the surrounding capillaries were filled with small mononuclear cells. In larger areas a single collecting tubule or group of convoluted tubules formed the center of a dense area of round cell infiltration . . . Collections of round cells were observed about the vessels in the intermediate zone and sometimes surrounding the vessels as they ran into the cortex." The preceding he regards as an early stage in the process. Of a more advanced stage he observes: "Masses of round cells in enormous numbers infiltrated the intertubular tissue extending in rays from the intermediate zone toward the capsule, occurring in great patches in the papilla." Concerning the origin he believes "it is probable that these round cells come from the circulating blood and not from the fixed connective tissue cells of the kidney, for in a number of sections the capillaries surrounding small foci of necrosis were seen to be filled with small mononuclear cells."

As previously stated the more chronic changes found in the kidneys of rabbits inoculated with streptococci are quite similar to those we have found in the kidneys of normal rabbits and also described by others.

Dickson, Ophüls, Harvey, O'Hara, Smith and Longcope believe they have to a greater or less degree, and by various means, produced a chronic nephritis in laboratory animals. The changes described by these writers are in general quite similar and correspond very well with those found in our series with the exception of the rather marked glomerular changes described by Dickson in the kidneys of guinea-pigs injected with uranium nitrate and the similar though less marked changes observed by Longcope in the kidneys of rabbits receiving repeated intoxicating doses of proteid.

In conclusion it is evident that the study of experimental nephritis in animals should be controlled by a thorough study of the kidneys of normal animals kept under similar conditions. We also believe that the best results will be obtained by the maintenance of the best sanitary surroundings for both sets of animals.

SUMMARY

Among the results are the demonstration of fewer changes in the kidneys of rabbits treated with antistreptococcus serum or vaccine than in those of untreated animals, and the presence of changes characteristic of chronic nephritis in a large number of animals inoculated with streptococci.

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[21] *Jour. Path. and Bact.*, 1911-12, 16, p. 95.
[22] *Arch. Int. Med.*, 1913, 12, p. 49.
[23] *Jour. Exp. Med.*, 1913, 18, p. 678.

The most important result, however, is the experimental production of alterations essentially subacute and quite like the acute interstitial nephritis in human kidneys caused by the acute infectious diseases complicated by or due to streptococcus infection. Then too, we wish to emphasize the great need of thorough study of the kidneys of control animals in any investigation of experimental nephritis.